**PATENT** 

## **DOCKET NO.: ISIS0002-102 (ISIS-4313)**

#### In the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

Please amend claims 78, 94-96, 98, 100-102, 121, 122, 127, 128, 133, 134, 139, 140, 146, 151, 152, 158, 170, 175, 180, and 181 as indicated below.

Please cancel claims 99, 145, 157, 159-164, and 169 as indicated below.

# 1-77. (canceled).

- 78. (currently amended) A composition comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides have a central portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages, wherein said central portions are base-paired with each other in said duplex; at least one of said first and said second oligonucleotides having portions flanking said central portions having chemical modifications which make them resistant to single-stranded nucleases, and wherein each of said first and said second oligonucleotides comprises a nucleotide sequence consisting from eight to fifty nucleoside subunits.
- 79. (previously presented) A composition comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides have a central portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages, wherein said central portions are base-paired with each other in said duplex; at least one of said first and said second oligonucleotides having portions flanking said central portions having chemical modifications which make them resistant to single-stranded nucleases and increase their affinity for the other oligonucleotide of the duplex.

- 80. (previously presented) The composition of claim 78, wherein said chemical modifications are phosphorothicate linkages or 2'-methoxy modifications.
- 81. (previously presented) An affinity matrix comprising the composition of claim 78.
- 82-92. (canceled).
- 93. (previously presented) A composition of claim 78, wherein one of said oligonucleotides has the nucleotide sequence of SEQ ID NO:8.
- 94. (currently amended) A composition comprising a duplex of a first oligonucleotide and a second oligonucleotide wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides include a portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages and wherein said portions are base-paired with each other in said duplex, and wherein each of said first and said second oligonucleotides comprises a nucleotide sequence consisting from eight to fifty nucleoside subunits.
- 95. (currently amended) A composition comprising a duplex of a first oligonucleotide and a second oligonucleotide wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides include a portion having at least four consecutive ribofuranosyl residues that are base-paired with each other in said duplex; and at least one of said first and said second oligonucleotides including a chemical modification that makes said oligonucleotide resistant to single-stranded nucleases, and wherein each of said first and said second oligonucleotides comprises a nucleotide sequence consisting from eight to fifty nucleoside subunits.
- 96. (currently amended) A composition comprising a duplex of a first oligonucleotide and a second oligonucleotide wherein said first and said second oligonucleotides are not covalently

linked, wherein each of said first and second oligonucleotides include a portion that is basepaired with each other in said duplex; and at least one of said first and said second oligonucleotides having a further portion that includes a chemical modification that increases the affinity of said oligonucleotide for the other oligonucleotide, and wherein each of said first and said second oligonucleotides comprises a nucleotide sequence consisting from eight to fifty twelve to thirty nucleoside subunits.

- 97. (previously presented) A composition comprising a duplex of a first oligonucleotide and a second oligonucleotide wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides include a portion having at least four consecutive ribofuranosyl residues and where said portions are base paired with each other in said duplex; and at least one of said first and second oligonucleotides includes a chemical modification that makes said oligonucleotide resistant to single-stranded nucleases and that increases the affinity for said oligonucleotide for the other of said oligonucleotides.
- 98. (currently amended) A composition comprising a duplex of a first oligonucleotide and a second oligonucleotide that are not covalently linked, wherein at least one of said first and said second oligonucleotides includes a chemical modification that makes said oligonucleotide resistant to single-stranded nucleases and that increases the affinity for said oligonucleotide for the other of said oligonucleotides, and wherein each of said first and said second oligonucleotides comprises a nucleotide sequence consisting from eight to fifty twelve to thirty nucleoside subunits.

### 99. (canceled).

100. (currently amended) A composition comprising a duplex of a first oligonucleotide and a second oligonucleotide that are not covalently linked, wherein at least one of said first and said second oligonucleotides includes a chemical modification that increases the affinity for said oligonucleotide for the other of said oligonucleotides, and wherein each of said first and said

second oligonucleotides comprises <u>a nucleotide sequence consisting</u> from <del>eight to fifty</del> <u>twelve to thirty</u> nucleoside subunits.

- 101. (currently amended) A composition comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides include a portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages, wherein said portions are base-paired with each other in said duplex, and wherein each of said first and said second oligonucleotides comprises a nucleotide sequence consisting from eight to fifty nucleoside subunits.
- 102. (currently amended) The composition of claim 101 wherein said one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from twelve to thirty subunits.

103-105. (canceled).

106. (previously presented) A composition comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein said first and said second oligonucleotides have a central portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages, wherein said central portions are base-paired with each other in said duplex; at least one of said first and said second oligonucleotides having portions flanking said central portions, said portions having chemical modifications which make them resistant to single-stranded nucleases, and wherein one of said oligonucleotides has the nucleotide sequence of SEQ ID NO:8.

107-116. (canceled).

117. (previously presented) The composition of claim 78 wherein said chemical modifications are phosphorothioate linkages.

- 118. (previously presented) The composition of claim 78 wherein said chemical modifications are 2'-methoxy modifications.
- 119. (previously presented) The composition of claim 78 wherein said chemical modifications are 2'-fluoro modifications.
- 120. (previously presented) The composition of claim 78 wherein said chemical modifications are 2'-O-methoxyethoxy modifications.
- 121. (currently amended) The composition of claim 78 wherein one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from twelve to thirty nucleoside subunits.
- 122. (currently amended) The composition of claim 78 wherein one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from fifteen to twenty-five nucleoside subunits.
- 123. (previously presented) The composition of claim 79 wherein said chemical modifications are phosphorothicate linkages.
- 124. (previously presented) The composition of claim 79 wherein said chemical modifications are 2'-methoxy modifications.
- 125. (previously presented) The composition of claim 79 wherein said chemical modifications are 2'-fluoro modifications.
- 126. (previously presented) The composition of claim 79 wherein said chemical modifications are 2'-O- methoxyethoxy modifications.

- 127. (currently amended) The composition of claim 79 wherein one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from twelve to thirty nucleoside subunits.
- 128. (currently amended) The composition of claim 79 wherein one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from fifteen to twenty-five nucleoside subunits.
- 129. (previously presented) The composition of claim 94 wherein said chemical modifications are phosphorothicate linkages.
- 130. (previously presented) The composition of claim 94 wherein said chemical modifications are 2'-methoxy modifications.
- 131. (previously presented) The composition of claim 94 wherein said chemical modifications are 2'-fluoro modifications.
- 132. (previously presented) The composition of claim 94 wherein said chemical modifications are 2'-O- methoxyethoxy modifications.
- 133. (currently amended) The composition of claim 94 wherein one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from twelve to thirty nucleoside subunits.
- 134. (currently amended) The composition of claim 94 wherein one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from fifteen to twenty-five nucleoside subunits.

- 135. (previously presented) The composition of claim 95 wherein said chemical modifications are phosphorothicate linkages.
- 136. (previously presented) The composition of claim 95 wherein said chemical modifications are 2'-methoxy modifications.
- 137. (previously presented) The composition of claim 95 wherein said chemical modifications are 2'-fluoro modifications.
- 138. (previously presented) The composition of claim 95 wherein said chemical modifications are 2'-O- methoxyethoxy modifications.
- 139. (currently amended) The composition of claim 95 wherein one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from twelve to thirty nucleoside subunits.
- 140. (currently amended) The composition of claim 95 wherein one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from fifteen to twenty-five nucleoside subunits.
- 141. (previously presented) The composition of claim 96 wherein said chemical modifications are phosphorothicate linkages.
- 142. (previously presented) The composition of claim 96 wherein said chemical modifications are 2'-methoxy modifications.
- 143. (previously presented) The composition of claim 96 wherein said chemical modifications are 2'-fluoro modifications.

- 144. (previously presented) The composition of claim 96 wherein said chemical modifications are 2'-O- methoxyethoxy modifications.
- 145. (canceled).
- 146. (currently amended) The composition of claim 96 wherein one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from fifteen to twenty-five nucleoside subunits.
- 147. (previously presented) The composition of claim 97 wherein said chemical modifications are phosphorothioate linkages.
- 148. (previously presented) The composition of claim 97 wherein said chemical modifications are 2'-methoxy modifications.
- 149. (previously presented) The composition of claim 97 wherein said chemical modifications are 2'-fluoro modifications.
- 150. (previously presented) The composition of claim 97 wherein said chemical modifications are 2'-O- methoxyethoxy modifications.
- 151. (currently amended) The composition of claim 97 wherein one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from twelve to thirty nucleoside subunits.
- 152. (currently amended) The composition of claim 97 wherein one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from fifteen to twenty-five nucleoside subunits.

- 153. (previously presented) The composition of claim 98 wherein said chemical modifications are phosphorothioate linkages.
- 154. (previously presented) The composition of claim 98 wherein said chemical modifications are 2'-methoxy modifications.
- 155. (previously presented) The composition of claim 98 wherein said chemical modifications are 2'-fluoro modifications.
- 156. (previously presented) The composition of claim 98 wherein said chemical modifications are 2'-O- methoxyethoxy modifications.
- 157. (canceled).
- 158. (currently amended) The composition of claim 98 wherein one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from fifteen to twenty-five nucleoside subunits.
- 159-164. (canceled).
- 165. (previously presented) The composition of claim 100 wherein said chemical modifications are phosphorothicate linkages.
- 166. (previously presented) The composition of claim 100 wherein said chemical modifications are 2'-methoxy modifications.
- 167. (previously presented) The composition of claim 100 wherein said chemical modifications are 2'-fluoro modifications.

- 168. (previously presented) The composition of claim 100 wherein said chemical modifications are 2'-O- methoxyethoxy modifications.
- 169. (canceled).
- 170. (currently amended) The composition of claim 100 wherein one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from fifteen to twenty-five nucleoside subunits.
- 171. (previously presented) The composition of claim 101 wherein said chemical modifications are phosphorothicate linkages.
- 172. (previously presented) The composition of claim 101 wherein said chemical modifications are 2'-methoxy modifications.
- 173. (previously presented) The composition of claim 101 wherein said chemical modifications are 2'-fluoro modifications.
- 174. (previously presented) The composition of claim 101 wherein said chemical modifications are 2'-O- methoxyethoxy modifications.
- 175. (currently amended) The composition of claim 101 wherein one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from fifteen to twenty-five nucleoside subunits.
- 176. (previously presented) The composition of claim 106 wherein said chemical modifications are phosphorothicate linkages.

- 177. (previously presented) The composition of claim 106 wherein said chemical modifications are 2'-methoxy modifications.
- 178. (previously presented) The composition of claim 106 wherein said chemical modifications are 2'-fluoro modifications.
- 179. (previously presented) The composition of claim 106 wherein said chemical modifications are 2'-O- methoxyethoxy modifications.
- 180. (currently amended) The composition of claim 106 wherein one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from twelve to thirty nucleoside subunits.
- 181. (currently amended) The composition of claim 106 wherein one of said first and said second oligonucleotides comprises a nucleotide sequence consisting from fifteen to twenty-five nucleoside subunits.